UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,242	07/30/2001	Stephen C. Ekker	09531-033001	2274

26191 7590 12/15/2003

FISH & RICHARDSON P.C.
3300 DAIN RAUSCHER PLAZA
60 SOUTH SIXTH STREET
MINNEAPOLIS, MN 55402

EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 12/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,242	EKKER ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-23,60-64 and 68-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23,60-64 and 68-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 9/11/03. The amendment has been entered. Claims 1-20, 24-59 and 65-67 have been cancelled. New claims 68-97 have been added. Claims 60 and 64 have been amended. Claims 21-23, 60-64 and 68-97 are currently pending in the instant application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action.

3. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment to the claims and/or applicant's persuasive arguments.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 3/18/03 was filed after the mailing date of the Non-final rejection, 3/12/03. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 21-23 remain rejected and new claims 68-82 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such

a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record.

7. Regarding new claims 68-82, these new claims all depend on claim 21 and are thus drawn to methods for producing a teleost embryo comprising a polynucleotide analogue wherein the polynucleotide analogue is present in an amount effective to reduce expression of a selected nucleic acid in said embryo. Therefore, the written description and enablement rejection of record also applies to the new claims.

Response to Arguments

8. Applicant's arguments filed 9/11/03 have been fully considered but they are not persuasive.

9. Applicants argue that the specification exemplifies the instant claims using more than a sufficient number of target nucleic acids and polynucleotide analogues. Specifically, Applicants assert that they examined the distribution within the embryo of a morpholino oligonucleotide (MO), a 3'-5' phosphoroamidate oligonucleotide, a 2'-O methyl RNA oligonucleotide, and 2 different peptide nucleic acids (PNAs). Applicants also assert that they exemplified reduced expression using 21 different polynucleotide analogues, both MOs and PNAs directed to 12 different selected nucleic acids which Applicants claim are representative of the claimed genus of nucleic acids present in a teleost embryo because they represent a number of different types of genes which are expressed in different tissues and at different times during embryonic development (see pages 6-7 of Applicants response).

10. In response, it is acknowledged that the applicants have adequately described a sufficient number of species of **polynucleotide analogues** encompassed by the claims because the

Applicants have described a morpholino oligonucleotide (MO), a 3'-5' phosphoroamidate oligonucleotide, a 2'-O methyl RNA oligonucleotide, and 2 different peptide nucleic acids (PNAs). However, the Applicants have not described a representative number of **target nucleic acid sequences** because the claims encompass possibly millions of different nucleic acids, considering that the claims encompass nucleic acids expressed in all teleost embryos that undergo meroblastic cleavage. This includes the nucleic acids expressed in all species of fish and amphibians embryos. Therefore, although the specification has described 12 different selected nucleic acids that are expressed in different tissues and at different times in development, it appears that all of the nucleic acids described are of one particular species of teleost embryo: the zebrafish embryo. It is respectfully pointed out that the claims encompass methods which require that the practitioner know the sequence of the target nucleic acid in order to design the polynucleotide analogue used in the method, as well as the time-point in embryonic development when the target gene is expressed in order to practice the claimed invention. In the instant case, the specification has only described 12 specific species of target nucleic acids which expressed in zebrafish embryonic development and has not described target nucleic acid sequences expressed in other types of teleost embryos. Therefore, the specification does not describe a sufficient number of target nucleic acid sequences to adequately describe the entire genus of target nucleic acid sequences encompassed by the claims

11. Claims 21-23 remain rejected and new claims 68-82 are also rejected under 35 U.S.C. 112, first paragraph (in view of the written description rejection above), as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Response to Arguments

12. Applicant's arguments filed 9/11/03 have been fully considered but they are not persuasive.

13. Applicants' argue (See p. 8-9 of the response) that the specification describes reduced expression of 12 different selected nucleic acids using 21 different polynucleotide analogues including both MOs as well as PNAs. Applicants also assert that the specification also describes uniform distribution in the embryo of 5 different polynucleotide analogues, including MOs, PNAs, 3'-5' phosphoroamidate oligonucleotides, and 2'-0 methyl RNA oligonucleotides. In addition, it is argued that a person of ordinary skill in the art can utilize the literature and sequence databases or recombinant nucleic acid libraries to identify additional nucleic acids that are expressed in a teleost embryo (emphasis added by Examiner). As an example, Applicants indicate that the sequence of the zebrafish genome is known and as available in public databases maintained by NCBI and the Wellcome Trust Sanger Institute. Applicants also point to Example 3 in the specification for a teaching on how to design the suitable polynucleotide analogues. Applicants also point to the Examples in the specification where they observed some degree of reduce expression in almost all of the 21 polynucleotides analogues tested. Therefore, Applicants contend, a person of ordinary skill would not need to screen undue numbers of polynucleotide analogues to identify those molecules falling within the scope of the claims.

14. In response, it is first respectfully pointed out that the instant claims are not enabled in view of the written description rejection described above. That is, because the specification has

not sufficiently described the genus of target nucleic acids encompassed by the claims, one of ordinary skill in the art would have to perform additional experimentation to first identify the target nucleic acid sequences which are not described before the claimed method could be practiced. As indicated above, it is acknowledged that the specification has adequately described the types of polynucleotide analogues encompassed by the claims, because the specification has described the MOs, PNAs, 3'-5' phosphoroamidate oligonucleotides, and 2'-0 methyl RNA oligonucleotides. However, the 12 different target nucleic acids described in the specification does sufficiently describe the entire genus of target nucleic acids encompassed by the claims because the 12 nucleic acids described are not a representative number of all target nucleic acid sequences expressed in the all teleost embryos. As mentioned above, the claims encompass all target nucleic acid sequences expressed in all teleost embryos; however, the 12 described nucleic acids appear to be all expressed in zebrafish embryos, without a clear description of any target nucleic acids expressed in any other teleost embryo. Regarding Applicants arguments that a person of ordinary skill in the art could utilize the literature and sequence databases or recombinant nucleic acid libraries to identify additional nucleic acids that are expressed in a teleost embryo (emphasis added by Examiner). It is respectfully pointed out that this is a clear indication that additional experimentation, specifically screening nucleic acid libraries, is required to identify target nucleic acid sequences encompassed by the claims. With respect to applicants' arguments that the zebrafish genome is available in public databases, it is respectfully pointed out that zebrafish is only one species encompassed by the claims, and is not a representative number of species encompassed by the claims. Regarding the teachings on how to design the polynucleotide analogues, it is acknowledged that once a target sequence is known it

would not be undue for one of skill in the art to design a polynucleotide analogue targeted to said nucleic acid sequence. However, as indicated above, the specification has not adequately described the target nucleic acid sequences encompassed by the claims. Therefore, without a clear description of a representative number of target nucleic acid sequences, one of ordinary skill in the art would not know how to practice the claimed invention without first performing an undue amount of additional experimentation in order to identify the target sequences.

15. Claims 60-64 remain rejected and new claims 83-97 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record.

16. Regarding the rejection of new claims 83-97, it is noted that these claims depend on claim 60 are thus drawn to methods for reducing expression of a selected nucleic acid in an animal comprising contacting said animal with at least two polynucleotide analogues complementary to different regions of the selected nucleic acid, wherein said at least two polynucleotide analogues are more effective at reducing expression of the selected nucleic acid than either of the two polynucleotide analogues alone. Therefore, the written description and enablement rejection of record also applies to the new claims for the reasons of record and the reasons indicated below.

Response to Arguments

17. Applicant's arguments filed 9/11/03 have been fully considered but they are not persuasive.

18. Applicants argue that the specification exemplifies (specifically, Examples 3, 18, 24, and 25) the methods of claims 60-64 using 3 different pairs of polynucleotide analogues with each pair directed to a different selected nucleic acid (See p. 12-13 of the response). Applicants argue that in each case a synergistic reduction in expression of the selected nucleic acid was observed. Applicants' point out that the specification discloses how to make polynucleotide analogues and how to test polynucleotide analogues for reduced expression of the selected nucleic acid. Applicants also assert that Applicants that they have reduced to practice 3 different species of the claimed genus of selected nucleic acids and 3 different species of the claimed genus of polynucleotide analogues. Applicants argue, given the high level of skill and knowledge in this art as well as the reduction to practice of- a representative number of species, they have met the written description requirement. Applicants submit that the rejection of claim 59 is moot, and respectfully request that the rejection of claims 60-64 under 35 U.S.C. 12, first paragraph, be withdrawn.

19. It is respectfully pointed out that the rejection is based on the lack of description of a representative number of polynucleotide analogues that, when used in combination, exhibit a synergistic effect with respect to their ability to reduce expression of the target nucleic acid sequence. Furthermore, the specification has not adequately described how to make the polynucleotide analogues which exhibit a synergistic effect when used in combination. It is

acknowledged that the specification has described 3 specific pairs of polynucleotide analogues, each pair directed to a different target sequence, and that these 3 specific pairs of polynucleotide analogues exhibit a synergistic effect when used in combination. It is also acknowledged that the specification has described how to make chemical modifications to polynucleotide sequences to produce polynucleotide analogues (such as methods of producing MOs, PNAs, 2'-O Me's, etc.). However, the claims encompass methods of reducing the expression of any target sequence in an animal using two polynucleotide analogues specific for a target sequence wherein the two polynucleotide analogues have a synergistic effect when used in combination. Therefore, in order to meet the written description requirement, the specification would have to describe how to make polynucleotide analogues specific to any target sequence, such that when used in combination, the polynucleotide analogues have a synergistic effect on inhibiting expression of the target sequence. Although the specification has described 3 different pairs of polynucleotide analogues that exhibit a synergistic effect when used in combination, the specification has not described how to design polynucleotide analogues specific to any target sequence of interest such that the polynucleotide analogues will have a synergistic effect when used together. Therefore, the specification has not described a representative number of "synergistic" polynucleotide analogues considering that the claims encompass being able to produce "synergistic" polynucleotide analogues for any target sequence of interest.

20. Claims 60-64 remain rejected and new claims 83-97 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record.

21. Applicants argue that the specification does, in fact, adequately describe a reduction in expression of a sufficient number of selected nucleic acids using a sufficient number of polynucleotide analogues to enable the instant claims 60-64. Applicants assert that the specification describes a synergistic reduction in expression of 3 different pairs of polynucleotide analogues directed to 3 different selected nucleic acids, and argue that the skills required to identify a selected nucleic acid sequence, design at least two polynucleotide analogues, and evaluate the polynucleotide analogues for their ability to reduce expression of the selected nucleic acid, are well within the purview of those of ordinary skill in the art. Applicants also argue that the specification provides additional guidance on designing and using pairs of polynucleotide analogues such as, for example, pages 14-16 of the specification.

22. In response, as indicated above, the specification has not adequately described a sufficient number of "synergistic" polynucleotide analogues, considering that the claims encompass synergistic polynucleotide analogues specific for any target sequence of interest and also considering that the specification has only described 3 specific pairs of polynucleotide analogues that have a synergistic effect when used in combination. Furthermore, as indicates above, the specification has not described to one of skill in the art how to make "synergistic" polynucleotide analogues specific for any target sequence of interest. Considering that it is not a matter of routine experimentation to make synergistic polynucleotide analogues, even in view of the guidance provided in the specification, one of ordinary skill in the art would have to perform

an undue amount of additional experimentation in order to be able to design "synergistic" polynucleotide analogues to any target sequence of interest.

Claim Rejections - 35 USC § 102

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21-23 remain rejected and new claims 68 and 71-74 are also rejected under 35 U.S.C. 102(b) as being anticipated by Barabino et al (Mech. Develop. 1997, 63:133-143. Listed in IDS as reference AJ).

As indicated in the previous Office Action, it is noted that the claims are very broad and encompass administering any polynucleotides analogue (such as an antisense polynucleotide) to any teleost embryo that undergoes meroblastic cleavage (claim 23 limits the embryos to, among others, zebra fish embryos).

Barabino teaches a method for producing a teleost embryo comprising a polynucleotide analogue, wherein said teleost embryo is a zebra fish embryo (which undergoes meroblastic cleavage) and wherein the polynucleotide analogue is present in an amount effective to reduce expression of a target nucleic acid in the embryo, by contacting the embryo with the polynucleotide.

Specifically, Barabino teaches using antisense oligonucleotides that are specific for the Alx gene (see abstract and p. 138, first column). The zebra fish embryos were cultured in the

presence of the antisense oligonucleotides, therefore, the antisense molecules were added to the surface of the embryos (see pg. 138, first column).

Additionally, Barabino teaches that the oligonucleotide is targeted to Alx mRNA (see p. 138, first column), that the oligonucleotide is targeted to a region of the mRNA that comprises the coding region (e.g., see Figure 1A, p. 134), and that the oligonucleotide is 20-30 bases in length (e.g., see antisense oligonucleotide Alx1a, Alx2a, or Alx3a, Figure 1A, p. 134). Thus anticipating the limitations of new claims 68 and 71-74.

Response to Arguments

24. Applicant's arguments filed 9/11/03 have been fully considered but they are not persuasive.

25. Applicants argue that contrary to Examiner's assertion, Barabino does not use a polynucleotide analogue as applicants' claims recite. Applicants assert that according to the present invention polynucleotide analogues are "chemically modified polynucleotides". Applicants argue that the 2'-deoxyoligonucleotides of Barabino are not polynucleotides analogues, thus Barabino does not anticipate the claimed invention.

26. In response, it is respectfully pointed out that the specification defines polynucleotide analogue as, "Polynucleotide analogues are chemically modified polynucleotides. Typically, polynucleotide analogues are formed by replacing all or portions of the five-carbon sugar-phosphate backbone of a polynucleotide with alternative functional groups in such a way that base pairing with a selected nucleic acid is maintained." (See p. 9, lines 25-28). It is noted however, that the phrase "Typically polynucleotide analogues are formed by replacing all or portions of the five-carbon sugar-phosphate backbone..." is not limiting. Therefore, the only

limiting definition supplied in the specification is "Polynucleotide analogues are chemically modified polynucleotides". Considering that the any chemical modification to an oligonucleotide would make the oligonucleotide a "polynucleotide analogue", the mere addition of a base to an oligonucleotide would constitute a chemical modification and result in a polynucleotide analogue. Therefore, the manufacture of the antisense 2'-deoxyoligonucleotides used by Barabino would require starting with an nucleotide base and chemically modifying that base by adding another base, then chemically modifying that two-mer by adding another base, and so on until the complete oligonucleotide was formed. This oligonucleotide, which would constitute a "chemically modified" oligonucleotide, would meet the definition of polynucleotide analogue, as broadly defined in the specification and would be a polynucleotide analogue. Additionally, Applicants have not indicated why the 2'-deoxyoligonucleotides taught by Barabino are not polynucleotide analogues. Therefore, Barabino teaches "polynucleotide analogues" (as defined by the specification) which can be used to reduce the expression of selected nucleic acids in a teleost embryo.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

27. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

28. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

29. Claims 21 and 69, 70, 75-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barabino et al (Mech. Develop. 1997, 63:133-143. Listed in IDS as reference AJ) in view of Monia et al. (US Patent 5,563,255).

Claim 21 is rejected for being anticipated by Barabino because Barabino teaches Barabino teaches a method for producing a teleost embryo comprising a polynucleotide analogue, wherein said teleost embryo is a zebra fish embryo (which undergoes meroblastic cleavage) and wherein the polynucleotide analogue is present in an amount effective to reduce expression of a target nucleic acid in the embryo, by contacting the embryo with the polynucleotide. Specifically, Barabino teaches using antisense oligonucleotides that are specific for the Alx gene (see abstract and p. 138, first column). The zebra fish embryos were cultured in the presence of the antisense oligonucleotides, therefore, the antisense molecules were added to the surface of the embryos (indicated above).

Barabino does not teach that the oligonucleotide is a targeted to the 5'UTR region of the target mRNA (claim 69), or that the oligonucleotide is targeted to the AUG region (i.e., initiation site) of the target mRNA (claim 70), or that the oligonucleotide used comprises modifications

such that it is an oligonucleotide comprising: 1) a morpholino-modified oligonucleotide (claim 75), 2) a 3'-5' phosphoroamidate oligonucleotide (claim 76), 3) a peptide nucleic acid (PNA) (claim 77), or 4) an 2' O-methyl group (claim 78).

However, Monia teaches that antisense oligonucleotides can be designed to target any region of the mRNA including, specifically, the 5'-UTR region (see column 5, lines 42-60), the translation initiation site (i.e., the AUG region in the mRNA) (see column 5, lines 50-60). Furthermore, Monia teaches that the oligonucleotides can comprise a number of different modifications such that the antisense oligonucleotide comprises: a morpholino-modified backbone, a phosphorothioamidate group, a peptide nucleic acid (PNA), and/or 2' O-methyl groups (see column 7 lines 8-41 and column10, lines 55-60).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Barabino and Monia to produce the polynucleotide analogues of the instant claims with a reasonable expectation of success. One of ordinary skill would have been motivated to make the claimed polynucleotides because Monia teaches that the 5'-UTR and AUG regions of the target mRNA are "preferred" regions to target (see col. 5, lines 42-65). Furthermore, Monia teaches that it is beneficial to modify the antisense oligonucleotides to so that the oligonucleotides are 1) more resistant to nucleases, 2) have improved uptake by the target cells, and 3) have increased binding affinity for the target mRNA (see col. 6 lines 19-30). Monia specifically indicates that the desired modifications include: a morpholino-modified backbone, a phosphorothioamidate group, a peptide nucleic acid (PNA), and/or 2' O-methyl groups (see column 7 lines 8-41 and column10, lines 55-60).

Conclusion

30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
AU 1635

DAVE T. NGUYEN
PRIMARY EXAMINER